PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* 15 JUNE 2004 (15.06.2004) | |
| Applicant's or agent's file reference OP04-1024 | FOR FURTHER ACTION See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| **PCT/KR2004/000774** | **02 APRIL 2004 (02.04.2004)** | 03 APRIL 2003 (03.04.2003) |

International Patent Classification (IPC) or both national classification and IPC

**IPC7 A61K 38/16**

Applicant

**REGEN BIOTECH, INC.. et al**

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.


Name and mailing address of the ISA/KR
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# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/KR2004/000774

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☒ in wirtten format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/KR2004/000774

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1 - 12 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 1 - 12 | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 9 - 12 | YES |
| | Claims | | NO |

2. Citations and explanations :

The following documents are referred to in this report.

D1: Int. J. Biochem. Cell Biol. Vol.29, No.5, pp.721-725, 1997
D2: J. Biol. Chem. Vol.277, No.48, pp.46159-46165, 2002
D3: J. Biol. Chem. Vol.275, No.40, pp.30907-30915, 2000

1. Novelty

The subject-matter of claims 1-12 is related to the use of peptides that interact with alpha v beta 3 integrin of endothelial cells. The said peptides are betaig-h3 itself and the fas-1 domains of betaig-h3. They inhibit endothelial cell adhesion and migration and, subsequently, have anti-angiogenic activity.
D1 discloses that alpha v beta 3 integrin mediates cell adhesion to extracellular matrix by recognizing the conserved arg-gly-asp(RGD) sequence of several plasma and matrix proteins and alpha v beta 3 is upregulated in response to vascular damage, during angiogenesis and in certain types of malignancy.
D2 discloses that all four of the fas-1 domains in betaig-h3 mediate MRC-5 fibroblast adhesion and this was specifically inhibited by a function-blocking monoclonal antibody specific for the alpha v beta 5 integrin.
D3 discloses that betaig-h3 proteins are highly active in mediating human corneal epithelial cell adhesion and spreading, and the functional receptor for betaig-h3 is alpha 3 beta 1 integrin.
None of D1-D3 discloses that betaig-h3 proteins with the sequences described in claims 1-12 of the present invention interact with alpha v beta 3 integrin of endothelial cells and inhibit endothelial cell adhesion, migration, and angiogenesis. Therefore, the subject-matter of claims 1-12 can be considered novel(Article 33(2) PCT).

2. Inventive Step

The fact disclosed in D2 and D3 that betaig-h3 proteins can interact with alpha v beta 5 integrin and alpha 3 beta 1 integrin does not imply the said proteins can also interact with alpha v beta 3 integrin since those integrins are known to be regulated by distinct growth factors in D1. (Continued on Supplemental Sheet)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of :

Box V.

Thus, those skilled in the art wouldn't be able to expect the betaig-h3 proteins with the sequences described in claims 1-12 can interact with alpha v beta 3 integrin to inhibit endothelial cell adhesion, migration, and angiogenesis. Therefore, the inventive step of claims 1-12 can be acknowledged(Article 33(3) PCT).

3. Industrial Applicability

The subject-matter of claims 1-8 relates to a method of therapeutic treatment. Concerning the assessment of the industrial applicability of the subject-matter relating to therapeutic applications, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims (Article 33(4) PCT).